Biologia Geral e Experimetal

Universidade Federal de Sergipe

São Cristóvão, SE 5 (2): 16-24 30.vii.2005

ELECTROPHYSIOLOGICAL EFFECTS OF SODIUM THIOPENTAL ON THE RIGHT ATRIUM OF THE RABBIT (*ORYCTOLAGUS CUNICULUS*)

Eduardo Antônio Conde-Garcia[1]
Marilene de Paula-Carvalho[1]
Antonio Edilson Nascimento[1]
Vanda Rodrigues de Oliveira[1]
Marcli Costa da Silveira Libório[1]

ABSTRACT

This study describes the effects of sodium thiopental (40 mg/l) on the rabbit atrium. The electrical endocardial signals and the intracellular action potentials were recorded. The results revealed a reduction in the atrial impulse velocity (from 75 ± 3 cm/sec to 63 ± 7 cm/sec), disorganization of the propagated electrical front wave, reduction of the spontaneous atrial pacemaker rate, depolarization of atrial cells (quiescent: 3.46 ± 1.2 mV; under electrical stimulation: 3.1 ± 0.5 mV), and an increase of the atrial cellular refractory period (from 52 ± 5 msec to 117 ± 8 msec). Atropine sulfate (1 mg/l) did not prevent or abolished the bradicardia produced by the sodium thiopental.

Keywords: Electrocardiophisiology, action potentials, atrial cells, sodium thiopental.

RESUMO

O estudo descreve os efeitos do tiopental sódico (40 mg/l) sobre átrios de coelho. Foram registrados os sinais elétricos endocárdicos e os potenciais de ação intracelulares. Os resultados mostraram redução da velocidade de propagação do impulso atrial (75 ± 3 cm/sec a 63 ± 7 cm/sec), desorganização da frente de onda propagada, redução da freqüência espontânea do marcapasso atrial, despolarização de células atriais mantidas em repouso (3.46 ± 1.2 mV) ou sob estimulação elétrica (3.1 ± 0.5 mV), e aumento do período refratário das células atriais (52 ± 5 msec a 117 ± 8 msec). O sulfato de atropina (1 mg/l) não preveniu ou aboliu a bradicardia produzida pelo tiopental sódico.

Palavras-chave: eletrocardiofisiologia, potencial de ação, células atriais, tiopental sódico.

INTRODUCTION

Sodium thiopental (NaTHIO) is a well-known barbiturate. Its rapid hypnotic properties derive from its effective liposolubility, a property due to the presence of a sulfur atom substituting an oxygen atom in the ureic residue of the barbiturate ring. At blood concentrations of up to 16 mg/ml, conscience is lost quickly (Evers & Crowder, 2001). Patients of normal body weight who receive small doses of NaTHIO normally wake up around 5 to 10 minutes later. Rapid recovery occurs as a consequence of the redistribution of NaTHIO among different tissues and organs, mainly those with high blood flow demands. In plasma, 85% of NaTHIO is bound to albumin molecules and, as a consequence, patients with severe hypoalbuminemia may need less NaTHIO to lose consciousness during anesthetic procedures.

Becker & Tonnesen (1978) reported some cardiovascular effects produced by NaTHIO in patients anesthetized exclusively by this drug. These effects included an increase in heart rate during the induction phase, a decrease in systolic blood pressure, and an increase of the ventricular pre-ejection period.

Since Beattie *et al.* (1930) showed that chloroform facilitates the appearance of ventricular fibrillation, the

[1] Departamento de Fisiologia, Laboratório de Biofísica do Coração. Universidade Federal de Sergipe, Av. Marechal Rondon, s/n, Jardim Rosa Elze, São Cristóvão, Se, 49100-000. egarcia@ufs.br

anesthetic side-effects have been investigated exhaustively. However, Price & Ohnishi (1980) have emphasized the need for a better understanding of the effects of NaTHIO on the conduction of electrical impulses and myocardial excitability.

This paper describes the electrophysiological effects promoted by this thiobarbiturate. The following parameters were studied: a) conduction velocity of the atrial electrical impulse, b) organization of the wave front of the propagated electrical impulse, c) spontaneous pacemaker rate, d) cellular resting potential in quiescent and electrically stimulated myocardial fibers, e) morphology of propagated action potentials, and f) electrical refractory period of the atrial cells. These parameters are especially important given the use of NaTHIO in animal research as a hypnotic drug or as an auxiliary to prevent ischemic/reperfusion-induced cardiac arrhythmias (Ruigrok *et* al., 1985; Schultz *et* al., 1997; Conradie & Coetzee, 1999; Kato & Foëx, 2002).

MATERIAL AND METHODS

The present study was carried out on adult rabbits (1.5-2.0 kg) of both sexes. Animals were sacrificed by a blow applied to the base of the skull. Their hearts were removed immediately and immersed in a modified Tyrode solution (in mM: NaCl 137, KCl 5.0, $MgCl_2$ 0.5, $NaHCO_3$ 12, $CaCl_2$ 1.8, Glucose 6.0, NaH_2PO_4 1.8). The right atrium was separated and mounted in a chamber with its endocardial surface facing upwards, superfused in Tyrode at 34.0±0.5°C (UNITEMP, model 111, FANEM, Cumbica, Guarulhos, Sao Paulo, SP), aerated and buffered with carbogen mixture (95% oxygen plus 5% carbon dioxide, <1% error). The test solution was prepared by adding NaTHIO (Thionembutal, Abbott, Laboratórios do Brasil, Ltda., São Paulo, SP) to the Tyrode.

Surface records were performed with the aid of a Teflon®-coated silver wire electrode (150 mm) inserted into a hypodermic stainless steel needle (length:100 mm, outer diameter: 1 mm) used as a grounded pole. The electrode was then mounted on a mechanical micromanipulator to allow it to be displaced smoothly (X-Y axes) along the endocardial surface. Electrical signals captured by this roving electrode were amplified differentially, monitored, and photographed by an oscilloscope camera (Differential Amplifier 5A22N, C-50 Oscilloscope Camera, D44 Dual Beam Oscilloscope, TEKTRONIX, Inc. Beaverton, Oregon, USA).

Intracellular readings were taken with 3M KCl-filled glass microelectrodes (DC resistance equal to 40 MW, tip diameter about 0.1mm: Oliveira-Castro & Machado, 1969). Microelectrode signals were sent to a high input impedance amplifier (M701, W-P Instruments, Inc., New Haven, Connecticut, USA) and then to a plug-in oscilloscope amplifier (5A48 Dual Trace Amplifier, TEKTRONIX, Inc. Beaverton, Oregon, USA). Following the experimental protocol, the atrium was stimulated electrically using ungrounded electrical current pulses (DS2 Isolator Unit, D4030 Pulse Programmer, DIGITIMER Limited, Welwyn Garden City, Hertfordshire, England). The stimuli were delivered through a pair of stainless steal electrodes placed at the right atrial appendage.

To evaluate the effect of thiobarbiturate on atrial impulse velocity, the atrial pacemaker frequency was set at a rate 20% higher than the spontaneous one. The conduction velocity was measured through previously selected pathways with uniform conduction of electrical signals. They were placed 4 to 6 mm from the stimulus electrodes to avoid interference of the stimulation field. Atrial impulse speed was estimated by displacing the surface electrode at constant steps (0.5 or 0.6 mm) and by simultaneous measurement of the time elapsed before the wave reached the electrode. It was possible to estimate the velocity of the atrial impulse by plotting each displacement against its corresponding time delay, based on the steepness of the regression line used to fit the experimental data.

To evaluate the effects of the barbiturate on atrial pacemaker activity, the electrical impulses recorded by

the surface electrode were counted, and the spontaneous rate was determined in detail (D4030 Pulse Programmer, DIGITIMER Limited, Welwyn Garden City, Hertfordshire, England; 1830 Interval Generator, 1832 Preset Control, 1831 Pulse Control Module, W-P Instruments, Inc. New Haven, Connecticut, USA).

To study the effects of NaTHIO on cellular resting potential, special care was taken with regard to the grounding system of the organ bath. For this, the silver electrode was covered with chloride, according to the technique described by Geddes (1972), in order to minimize junction potentials. This electrode, connected to the ground, was immersed in 3M KCl, with an agar/3M KCl bridge connecting it to the organ bath. The aim was to obtain electrical stability, and no electrical drift was recorded in the organ bath when the Tyrode voltage was monitored during 3 hours.

Statistical Analysis: Results are presented as means ± standard deviation. Student's t-test was used to analyze differences between means.

RESULTS

1. Effects of sodium thiopental on the propagated atrial electrical wave

Figure 1 shows two sets of electrical waves recorded from the atrial endocardium by moving the surface electrode at regular steps. The experiments were carried out on a paced right atrium (2 Hz). In the control (Figure 1A), the interval between successive waves was highly regular (electrode displacement step = 0.6 mm), indicating uniform propagation. Conduction velocity was calculated at 73 cm/sec ($r^2 = 0.9992$). In the experimental procedure (Figure 1B), waves were recorded in the presence of NaTHIO (40 mg/l). The surface electrode was displaced at steps of 0.5 mm and the impulse velocity of the atrium decreased to 56 cm/sec ($r^2 = 0.9954$, $p < 0.001$), 22% lower than the control value. Wave morphology was also less regular, and in several cases, irregularities indicate loose organization of atrial impulses. Figure 1C presents the regression lines for control and NaTHIO data points. Similar results were obtained for six other atria in which NaTHIO (40 mg/l) decreased the impulse velocity from 75 ± 3 cm/sec to 63 ± 7 cm/sec (n = 18 trials, $p < 0.001$). This effect had not disappeared completely 30 minutes after removal of the barbiturate from the organ bath.

2. Effects of sodium thiopental on the atrial pacemaker rate

At 60 mg/l, NaTHIO reduced the atrial pacemaker rate 16 to 47% (Figure 2). This negative chronotropic effect was eliminated partially or completely during the washout (n = 13 atria, 25 trials, $p < 0.001$).

At a doseage of 40 mg/l, NaTHIO decreased the spontaneous atrial rate progressively, and complete asystole was observed in several experiments (see Figure 3). Initial control rate was 158 bpm, but during NaTHIO (40 mg/l), it decreased progressively, sometimes to zero (interruptions in the fitting line). This effect was not altered by the application of atropine sulfate (1 mg/l, Sigma Chemical Co., St. Louis, MO, USA) 20 minutes before NaTHIO. However, removal of NaTHIO from the perfusion solution resulted in a return to the control rate. Similar results were obtained for three other atria (n = 6 trials). In some experiments, NaTHIO (40-60 mg/l) induced the appearance of isolated extrasystoles or even activated rapid ectopic foci (results not shown).

3. Effects of sodium thiopental on the resting potential of the myocardium

Figure 4 shows an intracellular record obtained from a quiescent atrial cell (resting potential = 81 mV). Downward pointing arrows indicate the moment when NaTHIO (40 mg/l) was added to the bath and upward arrows indicate when the barbiturate was removed from. NaTHIO promoted depolarization (3.46 ± 1.2 mV) when present in the solution bath. The depolarizing effect was not reverted completely by the washout. Similar effects were observed in five other atria (3.06 ± 1.4, n = 18 trials, $p < 0.001$).

NaTHIO (40 mg/l) also promoted depolarization in electrically stimulated atrial tissue (1.2 Hz). Figure 5

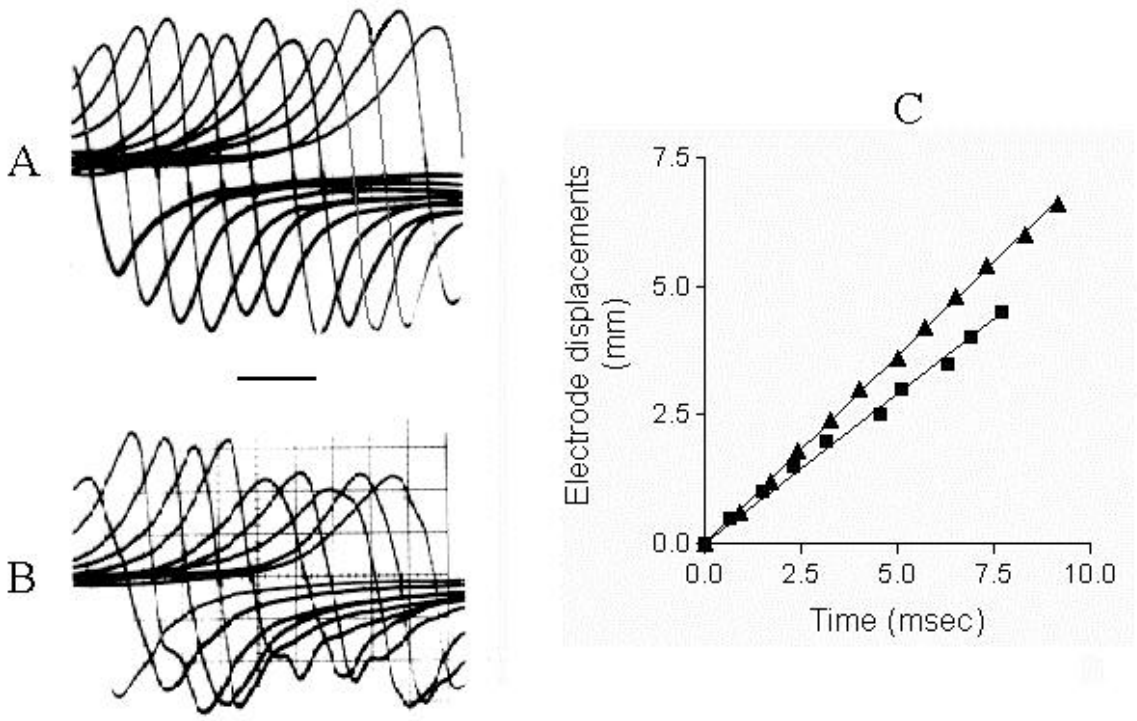

Figure 1. Effect of NaTHIO (40mg/l) on the rabbit atrial conduction velocity. Superimposed electrical waves recorded on the endocadial surface by displacing a surface roving electrode at constant steps. A: control (step=0.6mm); B: test solution (Tyrode + NaTHIO 40mg/l, step=0.5mm); Atrial impulse velocities were determined (C) by the steepness of regression lines. NaTHIO reduced the impulse velocity about 23 percent from 73cm/sec control (triangles, r^2=0.99) to 56cm/sec (squares, r^2=0.99, $p<0.001$). The experiment was carried out on paced atrium (2Hz, 34±0.1°C; Horizontal bar: 2msec).

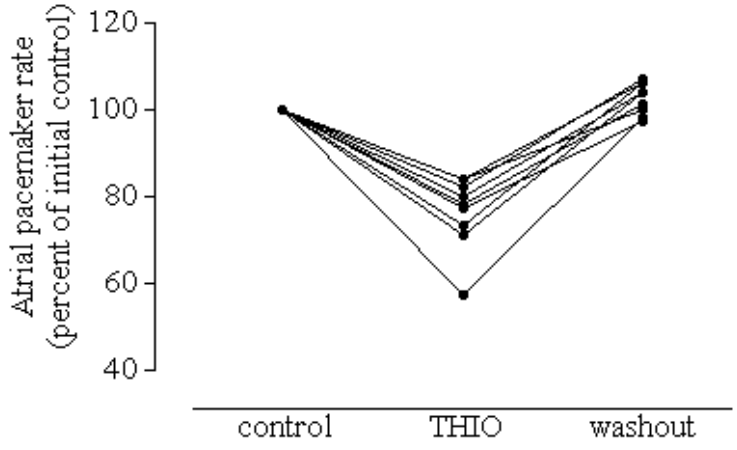

Figure 2. Negative chronotropic effect produced by NaTHIO (40mg/l) on the rabbit atrial pacemaker (n=13 atria). This effect ranged from 16 to 47 percent of the control rate. Experiments were performed on spontaneous beating atria (34±0.1°C, $p<0.001$).

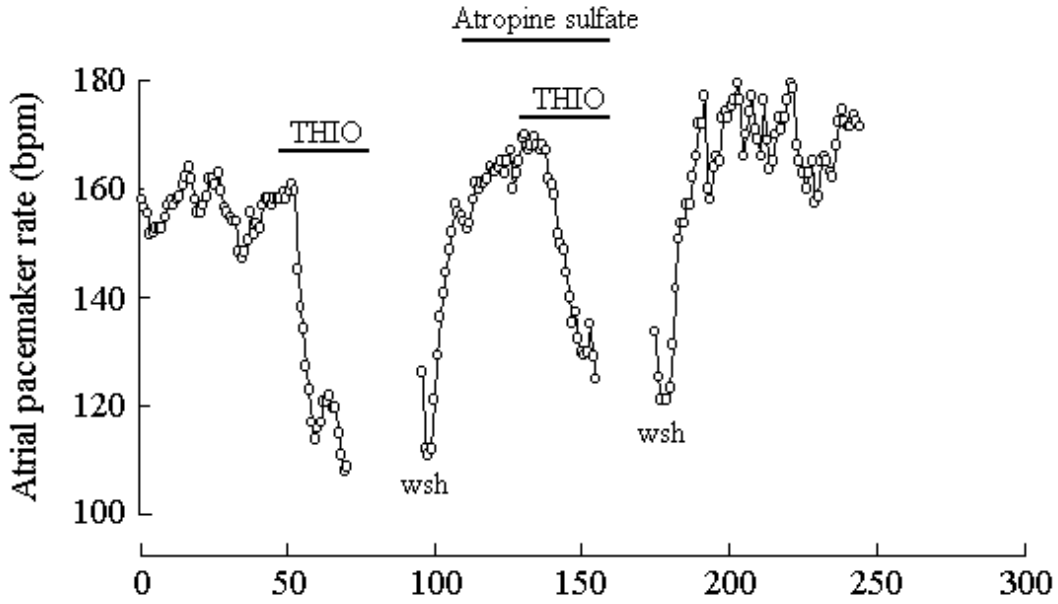

Figure 3. NaTHIO (40mg/l) induces asystole (interruption of the fitting line) in the rabbit right atrium. The asystole was observed in 4 of 13 rabbit atria assayed but bradycardia was present in all of them. This negative chronotropic effect could not be prevented by atropine sulfate (1mg/l) applied 20 minutes before and during the barbiturate action (2Hz, 34±0.1°C).

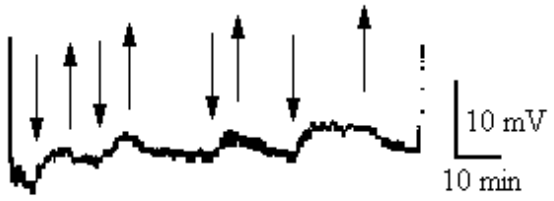

Figure 4. Effect of NaTHIO (40mg/l) on the quiescent rabbit atrial cell (initial resting potential=81mV). Downward and upward arrows mark when NaTHIO was added or removed, respectively, from the organ bath. Note that it produced small depolarizations (3.46±1.2mV). This effect was not completely abolished during washout (34±0.1°C).

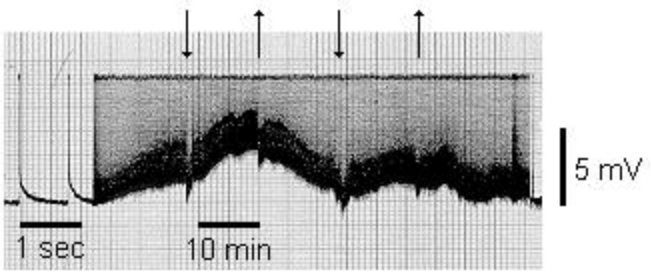

Figure 5. Effect of NaTHIO (40mg/l) on the resting potential of a rabbit atrial paced cell (1.2Hz). Thiobarbiturate depolarized the cell (downward arrows). Similar result was seen in other 5 atria (3.1±0.5mV, 34±0.1°C). Upward arrows stand for the washout.

shows intracellular records obtained from a stimulated atrium. The amplitude of action potentials is truncated due to the high gain needed for monitoring resting potential. Up and down arrows indicate, respectively, when NaTHIO (40 mg/l) was added to or removed from the bath. Note that NaTHIO induced depolarization. Similar results were obtained from five other atria (n = 12 trials) in which NaTHIO depolarized atrial cells 3.1 ± 0.5 mV ($p < 0.001$). Nevertheless, in contrast to the quiescent myocardium, recovery of control resting potential was faster in the paced atrium, and residual depolarization did not occur.

4. Effects of sodium thiopental on the morphology of the propagated action potential in atrial tissue

Figure 6 shows superimposed traces of action potentials that were randomly obtained from atrial cells located in a previously selected myocardium area (Zoom Stereo Microscope, model SZ-III, Olympus Optical Co., Ltd., Tokyo, Japan, ocular with embedded reticle). Control action potentials are seen in the Figure 6A, and Figure 6B presents action potentials recorded when NaTHIO (20 mg/l) was added to the external medium. Arrows indicate the maximum amplitude of the fast component of the myocardial action potentials. In the presence of NaTHIO, the amplitude of the fast component was reduced and was exceeded by that of the slow component (Paes de Carvalho *et al*., 1966, 1969).

5. Effects of sodium thiopental on the cellular refractory period

Figure 7 shows action potentials obtained from an atrial cell. The upper panel presents the control, and the lower panel depicts the effect of NaTHIO (40 mg/l) on the cellular refractory period. Extrasystolic stimuli, applied at different coupling intervals (between normal and premature stimuli), permitted measurement of the cellular refractory period. In the control, the refractory period was 73 msec, but it increased to 127 msec when NaTHIO was added to the bath. Similar results were

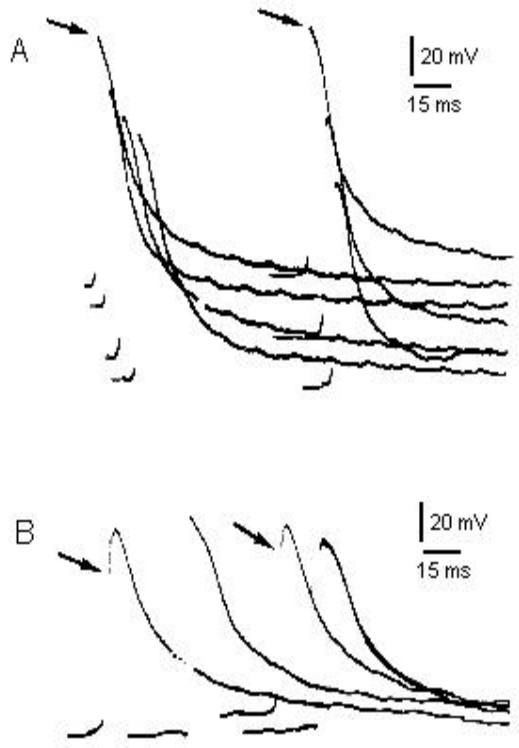

Figure 6. Superimposed traces of propagated action potentials obtained in different cell of the atrial endocardial suface. A: six action potentials recorded on control solution. All of them showed a well-developed fast component (depolarization phase). B: four action potential were recorded in the same atrial area, but after adding NaTHIO (40mg/l). Under the barbiturate action, several action potentials showed depressed fast components (arrows), suggesting a partial inhibition of the sodium current (34±0.1°C, stimuli: 30mV, 1ms, 2Hz).

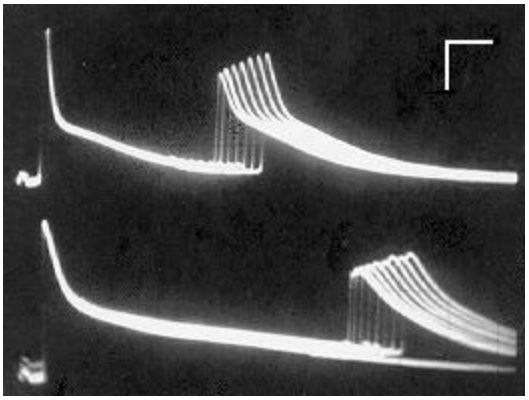

Figure 7. Effect of NaTHIO (40mg/l) on the cellular refractory period determined by applying extrasystolic stimuli with different coupling interval. Upper panel: control (refractory period equal to 73msec); lower panel: test with 40mg/l of NaTHIO (refractory period equal to 127msec). Experiment carried out at 34±0.1°C. Calibration bars: 20mV (vertical), 20msec (horizontal).

obtained in fifteen other cells (n = 4 atria; control : 52 ± 5 msec; test: 117 ± 8 msec; $p < 0.001$).

DISCUSSION

In spite of the development of new hypnotic agents, NaTHIO is still employed as an anesthetic in many experimental procedures with animals. This paper contributes to the understanding of its effects on the mammalian myocardium. The results showed that NaTHIO promotes arrhythmogenic effects similar to electrical wave front fragmentation, reduction of the fast component of action potential amplitude, and cellular depolarization. On the other hand, the increase of the refractory period may have an anti-arrhythmogenic effect associated with NaTHIO.

Our results show that NaTHIO promotes electrical changes in the myocardium that can promote and sustain cardiac arrhythmias. This is because it reduces the myocardium impulse velocity and simultaneously disorganizes the propagated wave front of the electrical impulse. This could facilitate the establishment of a chaotic state in electrical wave propagation. It is important to note that the irregular morphology observed in the surface records during NaTHIO action (Figure 1B) represents a form of wave front fragmentation that is a consequence of micro-accelerations and micro-deaccelerations of the propagated impulse. This facilitates re-entry mechanisms in the myocardium tissue, leading to the appearance of cardiac arrhythmia. The thiobarbiturate also decreased impulse propagation velocity, probably due to the decrease of the fast sodium currents that are responsible for the depolarization phase of propagated action potentials. This effect became clear because NaTHIO reduced clearly the fast component of the myocardial action potential (Figure 6B). Similar sodium current inhibition has been recorded for sodium pentobarbital (Wartenberg *et al*., 2001) – a close NaTHIO analogue.

Becker & Tonnesen (1978) observed a cardiac rate increase during the sleep induction phase in patients anesthetized with NaTHIO. However, in the isolated rabbit right atrium, this barbiturate promoted bradycardia, sometimes followed by an asystole. The tachycardic effect related by these authors could be explained by the depression of myocardial contractility, given that NaTHIO is known to reduce inward calcium flow in myocardial cells (Komai & Rusy, 1991, 1994a, 1994b; Park & Lynch, 1992; Housmans *et al*., 1995; Bettens *et* al., 1996; Descorps *et al*., 2001). This entry of calcium ions is important for the promotion of calcium-induced calcium release in the myocardial cells (Sitsapesan & Williams, 1994; Bassani *et* al., 1995; López-López *et* al., 1995; Sipido *et* al., 1998; Wier & Balke, 1999; Shannon *et* al., 2000; Bers, 2002) and initiatiation of the contractile process. Depression of myocardial contractility would lead to a decrease in arterial blood pressure, triggering a reflex response from the aortic pressure baroreceptors. Under such conditions, the sympathetic tonus of the heart would be enhanced and the cardiac rate increased. The depressor effect of NaTHIO on the atrial pacemaker cells does not seem to be mediated by release of acetylcholine from the parasympathetic nervous endings, given that the muscarinic blockade with atropine sulfate did not have any effect.

Our data suggest that NaTHIO modifies myocardial performance by acting on the ionic cellular currents responsible for electrogenesis in the cardiac tissue. To study this, resting potentials from quiescent and non-quiescent myocardial cells were measured (Figs. 4 and 5). In both cases, thiopental depolarized the myocardium. It is known that the resting potential is maintained by a complex balance between depolarizing currents, which are mainly carried by sodium and calcium ions, and hyperpolarizing currents, carried by potassium ions. The depolarizing effect of thiopental should thus be due either to an increase of the inward sodium-calcium current or to a decrease of the ouward potassium current. The depressor effect of NaTHIO on potassium channels was described recently (Pancrazio *et al*., 1993; Carnes *et al*., 1997; Martynyuk

et al., 1999). In fact, NaTHIO, as demonstrated elegantly by Heath & Terrar (1996), is a selective blocker of the K_s potassium channels (a subtype of the delayed potassium channel that is not sensitive to sotalol, a beta-adrenergic agonist). However, this channel is not involved in diastolic depolarization and thus does not appear to be related to the chronotropic effects of thiopental. It remains to be understood whether NaTHIO also enhances the inward rectifier conductance of the potassium channel (K_1) or reduces the slow inward sodium and calcium currents during the pacemaker action potential foot.

The increase in the refractory period observed during the action of NaTHIO is probably dependent on the blockade of the K_s channels. It is now well known that substances which reduce potassium conductance, such as amiodarone, 4-aminopyridine, dronedarone, tetraethylamonium, etc., also increase the tissue refractory period (Raatikainen *et* al., 2000; Workman *et* al., 2000; Li *et* al., 2001; Sun *et al*., 2002). These drugs produce long-lasting action potentials and lead to an increase of the effective tissue refractory period, and thus inhibit the re-entry circuits of myocardial tissues. Because thiopental is also able to prolong the action potential, it could act as an anti-arrhythmogenic agent in stressed myocardia.

In addition to its effects on the ionic currents carried by calcium and potassium, NaTHIO reduces the fast sodium inward current. This effect does not seem to be related to cellular depolarization because the changes in the membrane resting potential are of small magnitude (3 - 5 mV). Our results indicate that NaTHIO interferes, to a certain extent, with the fast sodium channels, contributing to a reduction in the atrial electrical wave velocity. Such effects lead to a decrease in the myocardial safety factor, which depends on the amplitude of the propagated action potential. This facilitates the appearance of impulse conduction blocks. If such effects predominate during the action of NaTHIO, the myocardium will become more vulnerable to the appearance of arrhythmias. However, cardiac behavior will ultimately depend on the balance of the pro- and anti-arrhythmogenic effects that are related to NaTHIO.

Acknowledgements ELETROBRÁS - Centrais Elétricas Brasileiras (Process Number 23113.009351/03-67) FAP-SE, FUNTEC FNS-MS - Fundação de Apoio à Pesquisa do Estado de Sergipe, Fundo Nacional de Saúde do Ministério da Saúde, Brasília/DF, Brazil (Process Number 01/2003) CNPq –Brazilian Research Council, Ministério da Ciência e Tecnologia, Federal Government, Brasilia/DF, Brazil.

REFERENCES

Bassani, J.W.M., W. Yuan & D.M. Bers, 1995. Fractional SR Ca release is regulated by trigger Ca and SR Ca content in cardiac myocites. **Am. J. Physiol.** 268:C1313-C1319.

Beattie, J., G.R. Brow & N.N.H. Long, 1930. Physiological and anatomical evidence for the existence of nerve tracts connecting the hypothalamus with spinal sympathetic centers. **Proc. R. Soc. Lond. B Biol. Sci.** 106:253-275.

Becker Júnior, K.E. & A.S. Tonnesen, 1978. Cardiovascular effects of plasma levels of thiopental necessary for anesthesia. **Anesthesiology** 49:197-200.

Bers, D.M. 2002. Cardiac excitation-contraction coupling. **Nature** 415:198-205.

Bettens, K.M., S.G. De Hert, S.U. Sys & D.L. Brutsaert, 1996. Role of the endocardial endothelium in the negative inotropic effect of thiopental. **Anesthesiology** 85:1100-1110.

Carnes, C.A., W.W. Muir III & D.R. Van Wagoner, 1997. Effect of intravenous anesthetics on inward rectifier potassium current in rat and human ventricular myocites. **Anesthesiology** 87:327-334.

Conradie, S., A. Coetzee & J. Coetzee, 1999. Anesthetic modulation of myocardial ischemia and reperfusion injury in pigs: comparison between halothane and sevoflurane. **Can. J. Anaesth.** 46(1):71-81.

Descorps-Declère, A., M.P. Sauviat, K. Samii & Y. Lecarpentier, 2001. Mechanical and electrophysiological effects of thiopental on rat cardiac left ventricular papillary muscle. **Br. J. Anaesth.** 86:103-109.

Evers, A.S. & C.M. Crowder, 2001. **General anesthetics, Goodman and Gilman's The Pharmacological Basis of Therapeutics.** 10th edition. McGraw- Hill, New York.

Geddes, L.A. 1972. **The electrode-electrolyte interlace, Electrode and the measurement of bioelectric events**. 1st edition. Willey Interscience, New York.

Heath, B.M. & D.A. Terrar, 1996. Separation of the components of the delayed rectifier potassium current using selective blockers of IKr and IKs in guinea-pig isolated ventricular myocites. **Exp. Physiol.** 81:587-

603.

Housmans, P.R., S.T. Kudsioglu & J. Bingham, 1995. Mechanism of the negative inotropic effect of thiopental in isolated ferret ventricular myocardium. **Anesthesiology** 82:436-450.

Kato, R. & P. Foëx, 2002. Myocardial protection by anesthetic agents against ischemia-reperfusion injury: an update for anesthesiologists. **Can. J. Anaesth.** 49(8):777-791.

Komai, H. & B.F. Rusy, 1991. Contribution of the known subcellular effects of anesthetics to their negative inotropic effect in intact myocardium. **Adv. Exp. Med.** 301:115-123.

Komai, H. & B.F. Rusy, 1994a. Effect of inhibition transarcolemmal calcium influx on content and releasability of calcium stored in sarcoplasmic reticulum of intact myocardium. **Adv. Pharmacol.** 31:215-221.

Komai, H. & B.F. Rusy, 1994b. Effect of thiopental on Ca^{2+} release from sarcoplasmic reticulum in intact myocardium. **Anesthesiology** 81:946-952.

Li D., L. Zhang, J. Kneller & S. Nattel, 2001. Potential ionic mechanism for repolarization differences between canine right and left atrium. **Circ. Res.** 88(11):1168-1175.

López-López, J.R., P.S. Shacklock, C.W. Balke & W.G. Weir, 1995. Local calcium transients triggered by single L-type calcium channel current in cardiac cells. **Science** 268:1042-1045.

Martynyuk, A.E., T.E. Morey, J.P. Raatikainen, C.N. Seubert & D.M. Dennis, 1999. Ionic mechanisms mediating the differential effects of methohexital and thiopental on action potential duration in guinea pig and rabbit isolated ventricular myocites. **Anesthesiology** 90:156-164.

Oliveira-Castro, G. & R.D. Machado, 1969. Control of glass microelectrodes for intracellular recordings. **Experientia** 25:556-558.

Paes de Carvalho, A., B.F. Hoffman & W.B. Langan, 1966. Two components of the cardiac action potential. **Nature** 211:938-940.

Paes de Carvalho, A., B.F. Hoffman & M. Paula Carvalho, 1969. Two components of the cardiac action potential. I. Voltage-time course and the effect of acetylcholine on atrial nodal cells of the rabbit heart. **J. Gen. Physiol.** 54:607-635.

Pancrazio, J.J., M.J. Frazer & C. Lynch III, 1993. Barbiturate anesthetics depress the resting K+ conductance of myocardium. **J. Phamacol. Exp. Ther.** 265:358-365.

Park, W.K. & C. Lynch III, 1992. Propofol and thiopental depression of myocardial contractility. A comparative study of mechanical and electrophysiological effects in isolated guinea pig ventricular muscle. **Anesth. Analg.** 74:395-405.

Price, H.L. & S.T. Ohnishi, 1980. Effects of anesthetics on the heart. **Fed. Proc.** 39:1575-1579

Raatikainen, M.J., T.E. Morey, P. Druzgala, P. Milner, M.D. Gonzalez & D.M. Dennis, 2000. Potent and reversible effects of ATI-2001 on atrial and atrioventricular nodal electrophysiological properties in guinea pig isolated perfused heart. **J. Pharmacol. Exp. Ther.** 295(2):779-785.

Ruigrok, T.J., A.M. Slade, P. van der Meer P, D. de Moes, D.M. Sinclair, P.A. Poole-Wilson & F.L.Meijler FL, 1985. Different effects of thiopental in severe hypoxia, total ischemia, and low-flow ischemia in rat heart muscle. **Anesthesiology** 63(2):172-178.

Schultz, J.J., A.K. Hsu & G.J. Gross, 1997. Ischemic preconditioning and morphine-induced cardioprotection involve the delta (delta)-opioid receptor in the intact rat heart. **J. Mol. Cell. Cardiol.** 29(8):2187-2195.

Shannon, T.R., K.S. Ginsburg & D.M. Bers, 2000. Potentiation of fractional SR Ca release by total and free intra-SR Ca concentration. **Biophys. J.** 78:334-343.

Sipido, KR, E. Carmeliet & F. van de Werf, 1998. T-type Ca^{2+} current as a trigger for Ca^{2+} release from the sarcoplasmic reticulum in guinea-pig ventricular myocites. **J. Physiol.** 508:439-451.

Sitsapesan, R. & A.J. Williams, 1994. Regulation of the gating of the sheep cardiac sarcoplasmic reticulum Ca^{2+}-release channel by luminal Ca^{2+}. **J. Membr. Biol.** 137:215-226.

Sun, W., J.S. Sarma & B.N. Singh, 2002. Chronic and acute effects of dronedarone on the action potential of rabbit atrial muscle preparations: comparison with amiodarone. **J. Cardiovasc. Pharmacol.** 39(5):677-684.

Wartenberg, H.C., J.P. Wartenberg & B.W. Urban, 2001. Human cardiac sodium channels are affected by pentobarbital. **European Journal of Anaesthesiology** 18:306-313.

Wier, W.G. & C.W. Balke, 1999. Ca2+ release mechanisms, Ca2+ spark, and local control of excitation-contraction coupling in normal heart muscle. **Circ. Res.** 85:770-776.

Workman, A.J., K.A. Kane & A.C. Rankin, 2000. Rate-dependency of action potential duration and refractoriness in isolated myocytes from the rabbit AV node and atrium. **J. Mol. Cell. Cardiol.** 32(8):1525-1537.

Aceito: 14.vii.2005